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Perspective

Pharmacological Options in the Treatment of Benign Prostatic Hyperplasia

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Basis for Pharmacological Intervention

Benign prostatic hyperplasia (BPH) is a common condition which currently accounts for more than 0.5 million transurethral prostatectomies performed worldwide each year, being the second most common operation performed on males over the age of 65. Recent estimates suggest that 30% of males over the age of 65 will require a prostatectomy during the remainder of their lifetime,[1] although the slow progress of the disease and the general acceptance of BPH as an inevitable consequence of aging result in perhaps as few as 20% of symptomatic men undergoing prostatectomy. Surgery, particularly transurethral resection of the prostate (TURP), is effective in the treatment of BPH, although a number of pharmacological approaches have been, and continue to be, assessed in the clinical setting.

In young adult males, the prostate gland is roughly the size of a walnut (weighing about 20 g) and is located at the bladder neck enveloping the urethra. It is considered to be a heterogeneous organ in which a widely accepted distinct zonal anatomy has been described by McNeal,[2,3] consisting of central, peripheral, and transition (and periurethral) zones and anterior fibromuscular stroma. BPH is characterized by increases in both glandular and fibromuscular tissue, with periurethral and transition zones of the prostate representing exclusive sites of initial hyperplastic growth.[4] Initially, BPH manifests as microscopic nodules in periurethral and transition zones (with periurethral nodules being mainly glandular and transition zone nodules mainly stromal) with progressive nodular proliferation leading to bladder outlet obstruction and/or symptomatic BPH (reduced urinary stream, nocturia, increased urinary retention, urgency, frequency, and postvoid dribbling). BPH is often considered a stromal disease since the ratio of stroma to epithelium increases from 2:1 in normal prostate to 5:1 in BPH.[5] It has been postulated that localized proliferation of stromal cells in the transition zone may represent the initial event in the pathogenesis of the disease, a process resembling embryonic dedifferentiation, and may be associated with mediators of stromal origin subsequently having paracrine effects on epithelial tissue.

In general, the relationship between prostatic size and urethral obstruction is poor, perhaps reflecting the fact that relatively small amounts of adenomatous tissue in the periurethral region can cause significant urethral obstruction. It is generally accepted that two components contribute to symptomatic BPH: a static component related to prostatic tissue mass and a dynamic component related to prostatic smooth muscle tone. In patients with BPH, it has been shown that complete blockade of the sympathetic outflow to the lower urinary tract reduces prostatic intraurethral pressure by nearly 50%.[6] These findings, together with the observation that prostatic smooth muscle density is related to the degree of outlet obstruction in patients with BPH, form the basis of pharmacological intervention designed to reduce prostatic smooth muscle tone. This is typified by the use of α_1 adrenoceptor antagonists.

Other approaches to BPH have sought to reverse the static component of obstruction due to the enlarged prostate. Such strategies may also alter the natural history of BPH; however, as disease progression is slow this has been difficult to prove. As long ago as 1895, White noted a decrease in prostatic size in 87% of men castrated for presumed BPH and in 50% of patients symptoms improved.[7] In 1944, Moore[8] reported that the absence of testicular function in men prior to age 40 prevented the development of BPH and also prostate cancer. These studies implicated testosterone, the major testicular and circulating androgen, in regulation

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of prostate growth and as a permissive or causative factor in the development of BPH and prostate cancer. In the prostate, testosterone undergoes reduction to 5α-dihydrotestosterone (DHT) through the action of steroid 5α-reductase enzyme activity,[9] such that DHT, which has 4−5-fold higher affinity for the androgen receptor than testosterone,[10] comprises approximately 90% of the total androgen.[11]

In 1974, Imperato-McGinley and co-workers described an inherited form of male pseudohermaphroditism secondary to 5α-reductase deficiency in the population of an isolated village in the Dominican Republic.[12] At birth the affected male children had female-like external genitalia, but at puberty growth of the phallus and descent of testes occurred, together with development of typical male musculature and male psychosexual orientation. However, the prostate remained small (approximately one-tenth the volume of that in age-matched controls[13]), and they had scanty facial hair and no temporal recession of the hair line. Subsequent work, recently reviewed,[14] showed that these individuals lacked or had a defect in a steroid 5α-reductase enzyme activity characterized by an acidic pH optimum. The enzyme was later cloned and designated as 5α-reductase 2.[15] Scientists at Merck realized the implications of the prostatic phenotype of the male pseudohermaphrodites and initiated the first medicinal chemistry project targeted toward the identification of inhibitors of prostatic 5α-reductase activity. This program resulted in the identification and subsequent development of finasteride (Proscar), which is currently the only 5α-reductase inhibitor approved for the treatment of BPH.

Two 5α-reductase enzymes have been identified and cloned, 5α-reductase 1 (5α-R1) and 5α-reductase 2 (5α-R2).[15] The major human prostatic 5α-reductase has been characterized as 5α-R2, for which finasteride is approximately 50-fold selective.[16] The 5α-reductase enzymes have different tissue distribution patterns, with 5α-R2 being found in prostate, genital skin, epididymis, seminal vesicles, and liver, while the type 1 enzyme is the predominant form in nongenital skin and is also present in the liver.[15] In the rat prostate, 5α-R1 is present at high levels, similar to or greater than those of 5α-R2,[17] and is localized to basal epithelial cells.[18] Whether 5α-R1 is also present in the human prostate remains unclear, with Russell being unable to detect it,[15] while other workers reported that the mRNA and enzyme activity are present.[19,20] Despite this controversy, much medicinal chemistry effort has focused on the identification of potent dual inhibitors of both 5α-R1 and 5α-R2 since DHT from the circulation may contribute to androgen action in the prostate, and this will be most effectively suppressed by inhibiting both 5α-R1 and 5α-R2, possibly resulting in improved efficacy compared with selective 5α-R2 inhibitors such as finasteride.[21]

While the presence of androgens and androgen receptors and the ability to convert testosterone to DHT through the action of 5α-reductase are absolute requirements for the development of BPH, a number of studies have shown that DHT has only minor effects on prostatic cells in culture, and the presence of other causative agents is strongly implicated.[4,21] Stromal−epithelial interactions appear to be important in this respect, and a number of growth factors (such as EGF, IGF, FGF, and TGF) may have a role in the pathogenesis of BPH (for review, see ref 22). Oestrogens have also been implicated in the development of BPH since changing levels associated with increasing age may affect androgen receptor density or stromal/epithelial cell death. Thus, while BPH development is age dependent and has an absolute requirement for the presence of DHT as a permissive factor, a definitive causative factor remains elusive.

Prostatic α_1 Adrenoceptors and Selective Antagonists

The prostate is innervated by cholinergic, adrenergic, and NANC nerves, although sympathetic noradrenergic innervation (*via* the hypogastric nerves and prostatic nerve plexus) is the primary determinant of prostatic smooth muscle tone. (It is also noteworthy that experimental denervation of the prostate leads to prostatic involution, and humans with spinal injury and impaired neuronal supply to the urinary tract do not develop BPH, suggesting neural input is important in the pathophysiology of the disease.[23]) A dense network of noradrenergic fibers has been found to supply the fibromuscular trabeculae of the gland, in which neuropeptides such as NPY may also coexist.[24] Both α_1 and α_2 adrenoceptors can be demonstrated by radioligand binding to prostatic tissue sections, although the latter subtype appears to be localized to glandular epithelium. Localization of α_1 adrenoceptors by quantitative receptor autoradiography using [^{3}H]prazosin indicates that the majority (85%) of α_1 adrenoceptor sites are on the fibromuscular stroma with a much lower density (15%) on glandular epithelium.[25] Based on other findings which show that stroma and glandular epithelium exist in a similar ratio, it can be estimated that >95% of α_1 adrenoceptors in human prostate are associated with stromal tissue. The properties of α_1 adrenoceptors from different regions of the prostate (anterior, posterior, lateral, and central) have been shown to be similar in terms of receptor affinity and density when assessed by [^{3}H]prazosin binding.[26]

Heterogeneity of α_1 adrenoceptors has been evident for some time with current nomenclature recognizing three subtypes (α_{1A}, α_{1B}, and α_{1D}), identified by molecular cloning (α_{1a}, α_{1b}, and α_{1d}) and having clearly defined native tissue correlates (see ref 27 for review). Additional heterogeneity is suggested on the basis of functional affinity estimates for a number of antagonists on a range of smooth muscle preparations which cannot be reconciled with their profile at currently classified α_1 adrenoceptors. All three human α_1 adrenoceptors have been cloned from human prostate by either RT-PCR of cDNA fragments or cDNA libraries, and sequencing of full length cDNAs shows a high degree of identity to other mammalian α_1 adrenoceptor homologs.[28,29] Using RNA extracted from human prostate, RNase protection assays have shown that the α_{1a} adrenoceptor subtype represents more than 70% of the total α_1 mRNA in human prostate.[28] *In situ* hybridization experiments have shown that α_{1a} mRNA localizes to the stromal compartment,[28] consistent with radioligand binding to prostatic tissue sections using receptor autoradiography,[25] although more recent *in situ* hybridization studies have also demonstrated α_{1a} mRNA in glandular cells, albeit with variability between different BPH samples.[30] Expression of different α_1 adrenocep-

Table 1. Antagonist Affinity Estimates (pA_2) for α_1 Adrenoceptor Antagonists Determined on Human Prostate and Binding Affinities (pK_i) at Cloned Human α_1 Adrenoceptor Subtypes[a]

antagonist	prostate pA_2	α_{1a}	α_{1b}	α_{1d}
prazosin	8.7	9.7	9.6	9.5
doxazosin	8.2	8.5	9.0	8.4
(+)-tamsulosin	8.2	8.4	7.0	8.1
(−)-tamsulosin	9.8	9.7	8.9	9.8
SL-89,0591	8.6	8.6	7.9	8.6
Rec-15/2739	8.8	9.0	7.5	8.6
WB-4101	8.9	9.8	8.6	9.6
5-methylurapidil	8.2	9.2	7.4	8.0
indoramin	8.7	8.4	7.4	6.8
SNAP-1069	7.9	7.8	6.7	6.1
SKF-104856	7.5	7.6	7.7	8.5
SNAP-5089	<6.5	8.7	6.9	6.8
BMY-7378	6.4	6.6	6.2	8.2
(+)-niguldipine	7.3	9.7	7.6	7.1
RS-17053	7.3	9.2	7.8	7.8
JTH-601	ND	9.4	8.9	8.9
KMD-3213	ND	10.4	7.7	8.7

[a] pK_i values determined by displacement of either [^{3}H]prazosin or [^{125}I]HEAT from recombinant α_{1a}, α_{1b}, and α_{1d} adrenoceptors. Prostatic pA_2 determinations carried out against norepinephrine and phenylephrine. Data from refs 39, 40, 44, 49, 56, 57, 59, 73, 75.

tors in different prostatic regions (apex, base, lateral lobe, and periurethral zones) appears to be similar when determined by Northern analysis,[31] although it must be emphasized that expression of high levels of mRNA for any given subtype does not necessarily correlate with high levels of receptor protein. Other techniques such as radioligand binding and functional analysis are important in this regard, especially since many native tissues have a heterogeneous population of α_1 adrenoceptors.

Using prostatic smooth muscle *in vitro* contractile responses to exogenous agonists are mediated almost exclusively *via* α_1 adrenoceptors, since α_2 agonists are relatively ineffective.[32] In addition, the ability of compounds such as prazosin and tamsulosin to antagonize field-stimulated contractions of isolated human prostate confirms the endogenous sympathetic innervation of these receptors.[33] Thus, selective α_1 adrenoceptor antagonists such as terazosin, doxazosin, and alfuzosin are effective in the treatment of BPH on the basis of their ability to lower prostatic tone and outlet resistance. In binding studies, both α_2 and non-adrenoceptor imidazoline binding sites have been identified, although a functional correlate for these receptors has not been demonstrated in human prostate. Some studies suggest that the density of α_1 adrenoceptor binding sites in hyperplastic prostate homogenates is higher than in corresponding non-BPH tissue, although this is not a consistent finding.[34,35] However, it is interesting to note that smooth muscle strips taken from hyperplastic prostatic tissues have been found to be more responsive to the α_1 agonist phenylephrine in comparison to normal tissue.[36] This may relate to the direct relationship between the extent of urinary flow improvement with α_1 adrenoceptor antagonist treatment and the density of prostatic smooth muscle mass.[37]

The pharmacological properties of human prostate tissue have been extensively studied in an attempt to characterize the functionally predominant α_1 adrenoceptor subtype (Table 1), although conclusions and findings have not been consistent.

In several studies, comparative functional affinity estimates for a range of α_1 antagonists against phenylephrine- or norepinephrine-mediated contractions of human prostate have been found to correlate highly with binding affinities at the cloned α_{1a} adrenoceptor.[38,39] These data are consistent with radioligand binding studies in which the affinity of α_1 adrenoceptor antagonists determined against [^{125}I]HEAT in human and canine prostatic tissue homogenates closely resembles affinities at cloned human α_{1a} adrenoceptors but not at α_{1b} or α_{1d} subtypes.[40] However, binding studies using other compounds such as oxymetazoline, prazosin, and the highly selective and potent α_1 adrenoceptor antagonist RS-17053 suggest that at least two α_1 adrenoceptor subtypes can be detected in prostatic homogenates.[31,41,42] Indeed, the relatively low affinity exhibited by prazosin in binding and functional studies using human prostate is not consistent with the affinity of this compound determined at cloned α_{1a}, α_{1b}, or α_{1d} subtypes, and one group has consistently maintained that the functional prostatic α_1 adrenoceptor is more characteristic of the previous pharmacologically described α_{1L} subtype.[41] This profile is exemplified by other highly potent and selective α_{1A} antagonists, such as SNAP-5089[43] and RS-17053,[44] which are both weak antagonists against α_1-mediated contractions of human prostate ($pA_2 \leq 7.0$) despite high affinity estimates for these compounds under identical experimental conditions against α_{1a}-mediated contractions of rat caudal artery and vas deferens ($pA_2 \geq 9.0$), and further suggests that the cloned α_{1a} adrenoceptor and the α_1 subtype mediating contractile responses of human prostate *in vitro* may be different. Importantly, RS-17053 differentiates between putative α_{1A} and α_{1L} adrenoceptors in the same species on preparations such as rat vas deferens ($pA_2 \sim 9.5$) and portal vein/anococcygeus ($pA_2 \sim 7.0$) illustrating that these effects are not species dependent. Further, similar findings have been reported for compounds such as Rec-15/2627 and Rec-15/2615, and across a wide range of structural analogs, functional affinity estimates on human prostate are much more consistent with potencies determined on tissues such as rabbit bladder neck, aorta, and urethra, all of which exhibit α_{1L} properties.[45]

These data raise the possibility that additional subtypes of the α_1 adrenoceptor exist, although extensive efforts have yet to identify molecular correlates for additional α_1 subtypes. However, genes encoding α_1 adrenoceptor subtypes possess introns, which raises the possibility of alternative isoforms derived by alternative splicing. Hirasawa et al.[29] have described the properties of two splice variants of the α_{1a} adrenoceptor, isolated from a human prostate cDNA library, which differ in length and sequence at the C-terminal end, and low levels of mRNA for both splice variants have been detected in several tissues. However, these variants of the α_{1a} adrenoceptor displayed similar binding affinities for several α_1 adrenoceptor antagonists, including high affinity for prazosin, suggesting that a molecular correlate of the α_{1L} subtype had not been isolated in this particular study. More recently, using human α_{1a} adrenoceptors expressed in CHO cells, Ford et al.[46] have reported differences in the affinity profile of several antagonists in membrane binding studies compared to whole cell binding. Indeed, binding affinities using

Table 2. Comparative Selectivity Profiles of α_1 Adrenoceptor Antagonists[a]

	pK_i				anesthetized dog ID_{50} (μg/kg)		
compd	α_{1a}	α_{1b}	α_{1d}	human prostate pA_2	IUP[b]	BP[c]	BP/IUP
prazosin	9.7	9.6	9.5	8.7	12	11	1
tamsulosin	9.7	8.9	9.8	9.8	2	1	0.5
terazosin	7.4	8.6	8.4	7.4	101	85	0.8
SL-89,0591	8.6	7.9	8.6	8.6	5	21	5
Rec-15/2739	9.0	7.5	8.6	8.8	4	109	30
RS-100,975	9.0	7.1	7.0	8.8	5	380	76
GG-818	9.7	7.8	7.6		13	7250	550

[a] Data from refs 47, 51, 54, 56, 57, and 59. [b] IUP, 50% reduction in intraurethral pressure in response to hypogastric nerve stimulation or agonist (phenylephrine or norepinephrine) administration. [c] BP, 50% reduction in agonist-induced pressor response. Binding affinities determined with either [^{3}H]prazosin or [^{125}I]HEAT using cloned expressed human α_{1a}, α_{1b}, or α_{1d} adrenoceptors.

whole cell binding techniques closely resembled functional affinity estimates for the same compounds, including RS-17053, at α_{1L} adrenoceptors on lower urinary tract tissues. Similar conclusions could be drawn based on antagonist potency against norepinephrine-mediated increases in inositol phosphate production in these cells. On this basis, α_{1L} pharmacology appeared to be exposed using the human α_{1A} adrenoceptor, although the mechanistic basis for this finding and how it relates to the functional properties of *in vitro* smooth muscle preparations are not clear.

Assessment of Prostatic Selectivity *in Vivo*

A number of established α_1 adrenoceptor antagonists are currently used in the management of BPH and are generally well tolerated at the doses used. However, high doses of this class of drug are associated with vascular events (postural hypotension, syncope, dizziness, headache, etc.). Clearly, α_1 adrenoceptor antagonists which have inherently greater selectivity for prostatic α_1 adrenoceptors offer the potential of increased urodynamic benefit. While this has yet to be established in the clinical setting, uroselectivity is apparent in various *in vivo* models. In the anesthetized dog, compounds which do not discriminate between α_1 adrenoceptor subtypes such as doxazosin, terazosin, and alfuzosin do not display uroselectivity,[47] although one study in anesthetized cats demonstrated a small degree of urethral selectivity for alfuzosin (particularly when administered intraduodenally) when urethral pressure and arterial pressure were elevated by continuous phenylephrine infusion.[48] Tamsulosin, while having some selectivity for prostatic α_1 adrenoceptors over the α_{1B} subtype, has been claimed to have inherent prostatic selectivity in the dog in one study,[49] although this is not a consistent finding, with the majority of studies indicating that this agent has a similar selectivity profile to compounds such as terazosin and doxazosin, albeit with greater potency.[47,50−54] Indeed, relative to these nonselective agents, much greater selectivity for prostatic α_1 adrenoceptors *in vivo* has been shown with more recent compounds on the basis of their selectivity profile at α_1 adrenoceptors. Thus, Rec-15/2739 blocks rises in intraurethral pressure (IUP) induced by either hypogastric nerve stimulation or phenylephrine at much lower doses than those required to block phenylephrine-induced pressor responses, showing about 30-fold selectivity in several anesthetized dog studies.[51,54,55] Other recent, and more selective, examples include RS-110,-975[56] and GG-818[57] (Table 2).

Prostate selectivity of agents such as Rec-15/2739 is clearly apparent under several experimental protocols using the anesthetized dog, although the compound has been found to be considerably more potent against agonist-induced blood pressure responses in rabbit (ED_{25} = 37 μg/kg, compared to 243 μg/kg in dog), thus exhibiting about 10-fold less uroselectivity in the rabbit compared to the dog.[49] Such findings highlight the well-documented species differences in the distribution of vascular α_1 adrenoceptor subtypes.[58]

Orthostatic blood pressure effects induced by α_1 adrenoceptor antagonists have been determined in 'tilt' or 'lift' models which predict well for the orthostatic effects observed with these agents in clinical studies. The lack of effect of GG-818, RS-100,975, and Rec-15/2739 at doses up to 10 mg/kg iv in models of orthostatic hypertension in rats contrasts with the activity of prazosin, terazosin, and tamsulosin, which produce orthostatic-induced falls in blood pressure at much lower doses in both rats and dogs (10−100 μg/kg).[49,56,57] Similarly, other potent and selective α_{1A} adrenoceptor antagonists such as SNAP-5150 and SNAP-5175 only induce postural hypotension at doses ≥ 1 mg/kg.[60]

α_1 Adrenoceptor Structure−Activity

Although the collection of α_1 antagonists presented in this section covers a range of structural types, all the compounds possess a central basic center flanked on at least one side by aromatic systems. Thus, the presence of a protonated form at physiological pH would appear to be a vital feature for α_1 antagonists. However, the precise profile in terms of subtype selectivity is heavily dependent on the nature of the basic center, the substitution of the aromatic rings, and the spatial orientation of the groups. The following overview separates the agents into structural classes defined by the basic center and discusses briefly how subtype selectivity varies within each series.

2,4-Diaminoquinazolines. Compounds within this series are typified by doxazosin, terazosin, alfuzosin, and prazosin, differing from one another through changes to the quinazoline 2-side chain. Although such modifications have profound effects on the potency and pharmacokinetic profiles, all of these quinazolines display essentially balanced binding profiles at cloned human receptors[54,61] (Table 3).

Doxazosin, terazosin, and alfuzosin are chiral and are marketed as the racemic mixtures. The two enantiomers of terazosin differ in that the *R*-enantiomer shows a greater level of selectivity for α_1 over α_2 receptors than either the *S*-enantiomer or the racemate.[62]

Very few novel quinazolines for the treatment of BPH have emerged recently, although Recordati has claimed a series of piperazine- and piperidine-linked derivatives,

Table 3. Binding Affinities (pK_i) of Quinazolines at Cloned Human α_1 Adrenosubtypes

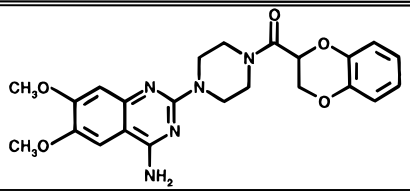
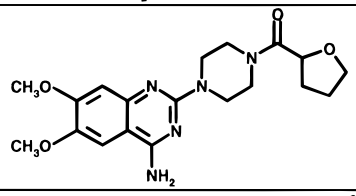
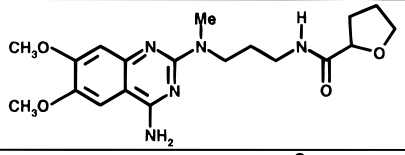
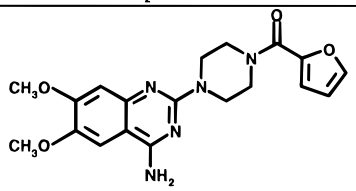
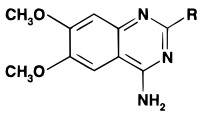
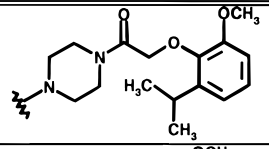
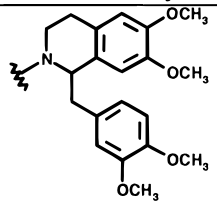
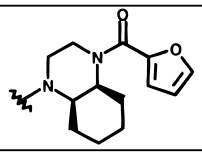
Name	Structure	pK_i		
		α_{1a}	α_{1b}	α_{1d}
doxazosin		8.5	9.0	8.4
terazosin		8.2	8.7	8.6
alfuzosin		8.0	8.0	8.5
prazosin		9.7	9.6	9.5

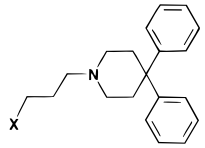
Table 4. Binding Affinities of Quinazolines at Mammalian α_1 Adrenosubtypes

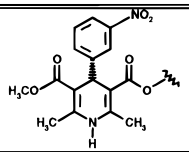
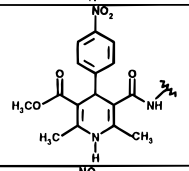
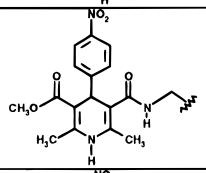
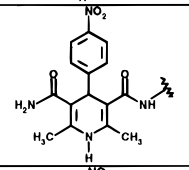
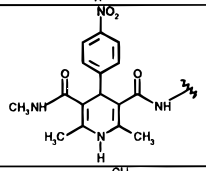
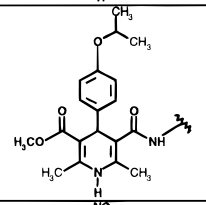
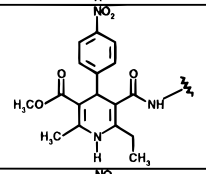
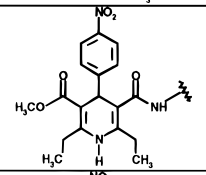
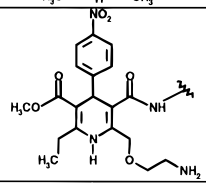


Name/No.	R	IC_{50} (nM) (unless otherwise stated)		
		Cloned α_{1a} (bovine)	Cloned α_{1b} (hamster)	Cloned α_{1d} (rat)
(1)		17.2	1.2	22.9
(2)		950	206	1550
(+)-cyclazosin		7.6[a]	9.7[a]	7.5[a]

[a] pK_i

Table 5. Binding Affinities (pK_i) of Dihydropyridine-Based Piperidines at Cloned Human α_1 Adrenosubtypes



Name/No.	X	pK$_i$		
		α_{1a}	α_{1b}	α_{1d}
(S)-(+)-niguldipine		9.80	7.26	7.00
SNAP-5089		9.63	7.87	7.18
(3)		8.23	7.19	6.84
SNAP-5150		8.73	6.48	6.40
(4)		8.5	6.38	6.21
(5)		7.16	6.76	6.05
(6)		9.18	6.83	6.69
(7)		8.90	6.55	6.35
SNAP-5399		9.19	6.49	6.20

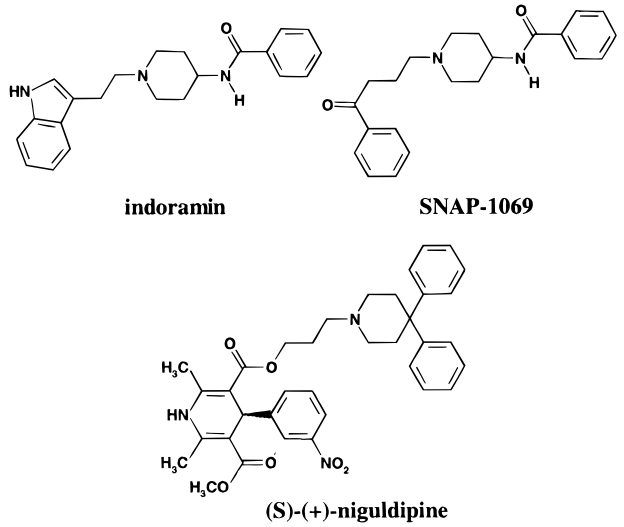


Figure 1.

e.g., **1** and **2**, that display few side effects as a result of increased selectivity for α_{1b} over α_{1d} mammalian cloned receptors (Table 4).[63] In addition, (+)-cyclazosin (Table 4), a prazosin derivative in which the piperazine linker is fused onto a cyclohexane ring, displays significant binding selectivity for α_{1b}.[64]

Piperidines. Indoramin is the first generation of piperidine-based α_1 subtype-selective antagonists used in BPH (Figure 1).[65] A significant drawback with indoramin, however, is its interaction with other receptors, in particular 5-HT and histamine, leading to sedation as a side effect. The major challenge within this class has been to improve upon the levels of α_1 subtype selectivity seen with indoramin while removing the polypharmacology. The majority of the work carried out in this area has been by the combined groups of Synaptic and Merck, and the second-generation compound SNAP-1069, where the indole terminus has been replaced by a phenyl ketone, does indeed display >10-fold selectivity for α_{1a} over α_{1b} and α_{1d}.[39] SNAP-1069 still suffers, however, from a broad spectrum of activities.

Further refinement of the piperidine class has been realized with an extensive series of compounds based on the calcium channel blocker (*S*)-(+)-niguldipine. In this program, a number of exquisitely α_{1a}-selective compounds have been identified through alteration of the 2- and 6-substituents of the dihydropyridine ring, replacement of the ester groups by amides, and variation of the mode of substitution of the 4-phenyl ring. Indeed, simply by remaining within the 4-(*p*-nitrophenyl) series, much of the calcium antagonist activity of the dihydropyridine nucleus could be suppressed.[66]

As Table 5 indicates, replacement of the C3-ester group in niguldipine by an amide linkage is well tolerated. However, extension of the linker chain to four methylene units as in compound **3** leads to a 25-fold reduction in α_{1a} affinity. C5-Amides SNAP-5150 and **4** maintain selectivity, albeit with a 10-fold loss in potency, and replacement of the nitro group at the C4-phenyl substituent by isopropyloxy (compound **5**) is poorly tolerated. Methyl substitution at the C2- and C5-methyl groups of SNAP-5089 boosts α_{1a} selectivity (compounds **6** and **7**), and the profile of the (aminoethoxy)methyl derivative SNAP-5399 is particularly compelling. The single enantiomers of SNAP-5399 have been profiled, and this has revealed that much of the binding selectivity resides in the (−)-isomer. The (aminoethoxy)methyl 2-side chain is present in the calcium antagonist amlodipine and is reponsible for its excellent pharmacokinetic profile. Amlodipine itself is inactive as an α_1 adrenoceptor antagonist, as might be predicted from the absence of the 4,4-diphenylpiperidine pharmacophore. This contrasts with the β-ketoamide synthetic precursor **8** to the Synaptic series which possesses significant α_{1a} activity (Figure 2).

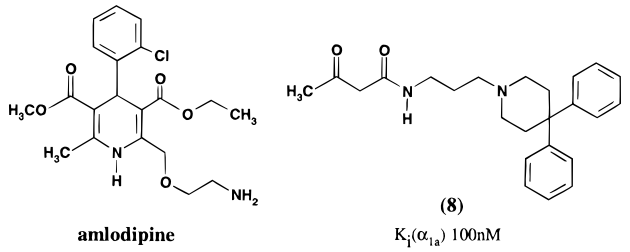


Figure 2.

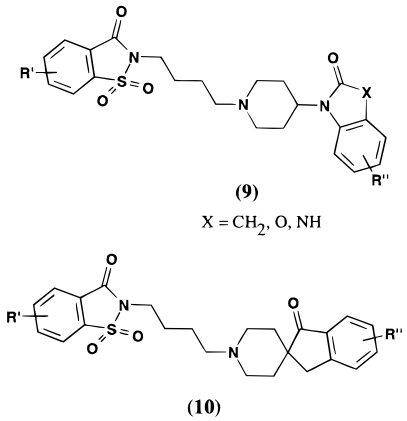


Figure 3.

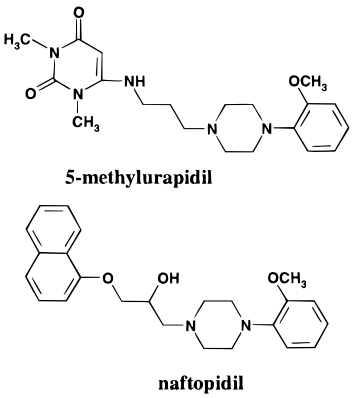
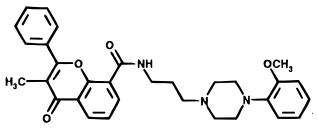
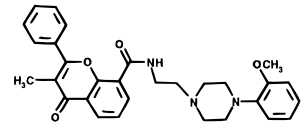
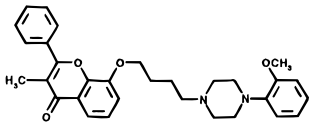
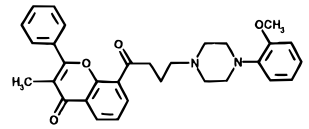
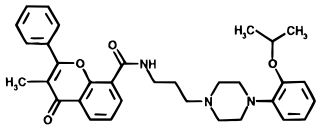
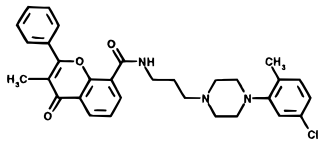
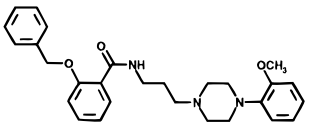


Figure 4.

SNAP-5399 is reported to inhibit the phenylephrine-induced contraction of dog prostate with a K_B of 1.4−1.5 nM.[67] However, in our experience, the niguldipine-derived series has displayed disappointing levels of functional potency on human prostate preparations.

A recent patent from Merck[68] claims a series of piperidine derivatives linked to a saccharin-based nucleus as displaying 30−500-fold selectivity for binding to cloned human α_{1a} receptors over α_{1b} and α_{1d} as well as at least 300-fold selectivity for α_{1a} over any other receptor type (Figure 3). No functional data for these compounds were disclosed, and general structures **9** and **10** are shown.

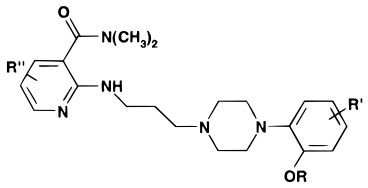
Table 6. Binding Affinities (IC_{50}) and *in Vivo* Profile of Rec-15/2739 and Related Compounds[a]

Name/No.	Structure	IC_{50} (nM)		ED_{25} (diastolic blood pressure) ID_{50} (urethral pressure)
		α_{1A}	α_{1B}	
Rec-15/2739		2	24	100
(11)		14	79	14
(12)		10	39	13
(13)		1.5	24	39
(14)		1	108	
(15)		1	29	
(16)				16

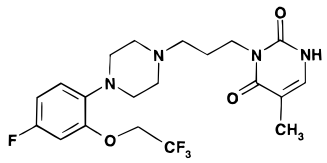
[a] Binding affinities were determined for CEC-pretreated rat hippocampus (α_{1A}) and rat liver (α_{1B}). *In vivo* selectivity was determined by comparing the dose (iv) required for 50% inhibition of norepinephrine-mediated contraction of proximal urethra (ID_{50}) with the dose (iv) required for 25% reduction in systolic blood pressure (ED_{25}) in anesthetized dogs.

Piperazines. The two main agents to appear within the piperazine class of compounds are Rec-15/2739 and SL-89,0591, and both are closely related to the earlier compounds 5-methylurapidil and naftopidil (Figure 4). In the Recordati series, selectivity for α_{1A} over α_{1B} was determined by comparing the binding affinities of the compound for CEC-pretreated rat hippocampus and rat liver.[69]

Rec-15/2739, as shown in Table 6, displays 12-fold selectivity for the α_{1A} preparation. The further examples in Table 6 **(11**−**15)** demonstrate that, in general, alteration in the length or nature of the linker leads to diminished selectivity, except for **13**, where the ether oxygen has been replaced by a keto group. *In vivo* in the anesthetized dog, however, the selectivity for inhibition of norepinephrine-mediated contraction of proximal urethra over effect on diastolic blood pressure is significantly greater for Rec-15/2739. Variations to the substitution pattern on the aryl ring have also been studied. Most notably, replacement of the 2-methoxyphenyl substituent by 2-(isopropyloxy)phenyl or 2-methoxy-5-chloro (compounds **14** and **15**) led to enhanced



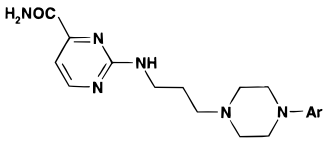
(20)

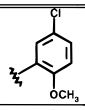


RS-100,975

Figure 5.

Table 7. Selectivity of SL-89,0591 and Related Compounds Determined by Comparison of the Dose (i.a.) Required To Produce a 20% Reduction of Mean Blood Pressure in the Rat (ID_{20}(arterial pressure, rat)) with the Dose (iv) Required for 50% Inhibition of Norepinephrine-Mediated Contraction of Proximal Urethra in the Cat (ID_{50}(urethral pressure))

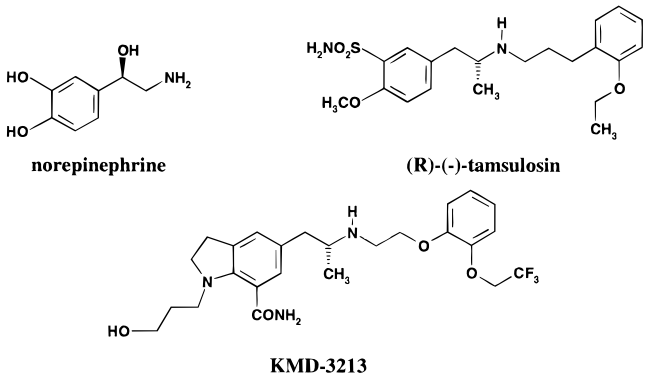


Name/No.	Ar	ID_{20} (arterial pressure, rat) / ID_{50} (urethral pressure, cat)
SL-89.0591		46
(**17**)		31
(**18**)		18
(**19**)		4

binding selectivity although the *in vivo* profiles were inferior to that of Rec-15/2739 (data not included). Recently, 16-fold selectivity *in vivo* has been claimed for **16** where the benzopyranone nucleus has been replaced by a benzamide derivative.[70]

The influence of the aryl substitution pattern has a dramatic effect on selectivity with other arylpiperazine series. For example, in the Synthelabo series, the 2-methoxy-5-chlorophenyl motif of SL-89,0591 (Table 7) was found to be optimal.[71] Noticeable reductions in potency (5−10-fold) were seen in this series when the linker chain was shortened from a trimethylene to a dimethylene unit.

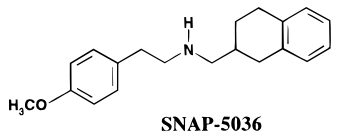
Most recently, a patent from Hofmann La Roche/Syntex covers a series of compounds **(20)** closely related to SL-89,0591, where functional prostatic selectivity is claimed along with reduced orthostatic effects in rat (Figure 5).[72] In addition, the same group has disclosed the structure of RS-100,975 (Figure 5) which is claimed to display ca. 100-fold selectivity for cloned human α_{1a} receptors over α_{1b} and α_{1d} as well as 76-fold uroselectivity in the anesthetized dog model.[56]



norepinephrine (R)-(-)-tamsulosin

KMD-3213

Figure 6.



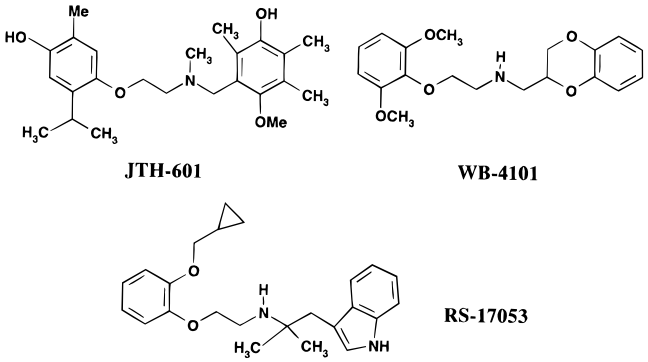
SNAP-5036

pK_i (human clones)

α_{1a}	α_{1b}	α_{1d}
8.4	7.4	6.8

pA_2 (human prostate) 6.6

Figure 7.



JTH-601 WB-4101

RS-17053

Figure 8.

Phenethylamines and Related Compounds. The phenethylamines, typified by tamsulosin and KMD-3213,[73] are structurally the most closely related to the endogenous agonist norepinephrine (Figure 6). The absolute stereochemistry at the methyl-bearing carbon has a significant impact on the pharmacological profile of these compounds, and (*S*)-(+)-tamsulosin displays a greater level of subtype selectivity, albeit with at least 10-fold reduction in potency compared with the *R*-(−)-enantiomer. Interestingly, a subtype-selective compound from Synaptic (SNAP-5036)[74] can be regarded as a substituted phenethylamine lacking the β-methyl group altogether (Figure 7). However, the translation to functional prostatic potency with SNAP-5036 is disappointing.

Related compounds are shown in Figure 8, where the linker between the aromatic ring and the basic amine is truncated (JTH-601)[75] or extended (WB-4101, RS-17053)[44] and maintains excellent levels of binding selectivity, although this does not translate to good functional prostatic potency in all cases (see Table 2). The influence on selectivity of the conformation adopted by these acyclic amines is emphasized by the profile of SKF-104856 shown in Figure 9 (see Table 1). In this case, the phenethylamine has been incorporated into a benzazepine framework, and the compound displays ca. 10-fold selectivity for the α_{1d} subtype.

Most recently, Glaxo[57,76] has published a patent on a series of compounds closely related to tamsulosin, where conformational constraint is introduced into the tri-

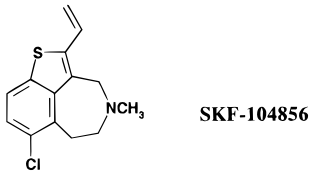


Figure 9.

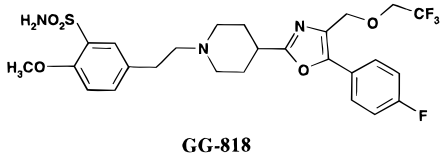


Figure 10.

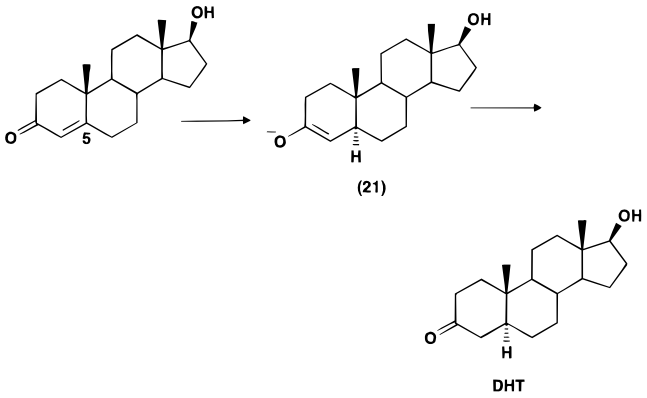


Figure 11.

methylene-linking chain (Figure 10); 550-fold prostate selectivity in the anesthetized dog is claimed for compound GG-818. In common with the selective agents RS-100,975 and KMD-3213, GG-818 houses a trifluoroethoxy substituent, suggesting this group may be a key structural element for prostate selectivity.

5α-Reductase Inhibitors: Structure−Activity Relationships

This section focuses on the main series of 5α-reductase inhibitors which are of use in the treatment of diseases where DHT is implicated. A review on the structural classes of 5α-reductase inhibitor was recently published by Frye[77] to which the reader is referred for a discussion of early developments in the field. A review by Abell is also useful, in particular for an account of the activity of compounds versus 5α-reductase from different animal species.[78] This section will focus mainly on the SAR of the newer dual inhibitors of both human 5α-reductase isozymes. Mention will also be made of the new 5α-reductase 1-selective compounds which have potential in the treatment of acne, hirsuitism, and male pattern baldness.

Enzyme Mechanism

5α-Reductase is an NADPH dependent membrane-bound enzyme which operates *via* delivery of the *pro-S*-hydrogen of the cofactor to the less hindered α-face of the substrate testosterone. The enolate **21** thereby generated is stabilized by the enzyme and subsequently protonated to generate DHT (Figure 11).

The kinetic mechanism is believed to proceed *via* a preferentially ordered binding of substrates and release of products from the enzyme[79] (Figure 12). Compounds may give rise to alternative types of inhibition by

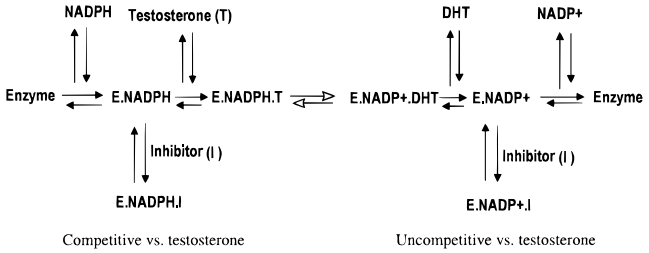


Figure 12.

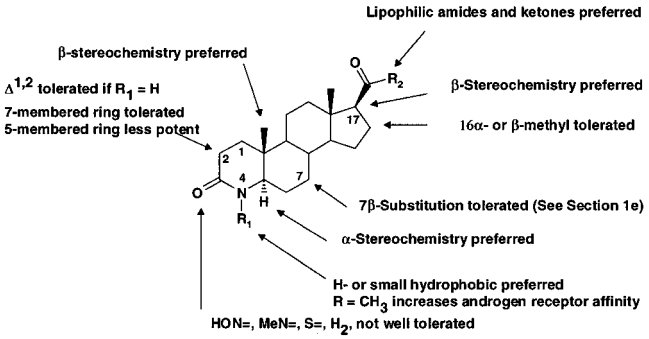


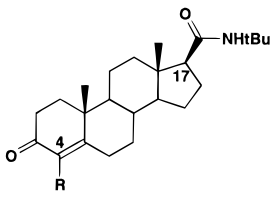
Figure 13.

interacting with different enzyme complexes in the sequence (Figure 12). In general, the azasteroid inhibitors discussed below interact with the enzyme−NADPH complex and are competitive with respect to testosterone, although some have now been found to be slow offset, essentially irreversible inhibitors (see below). The steroidal carboxylic acids are generally uncompetitive inhibitors which are believed to interact preferentially with the enzyme−$NADP^+$ complex.[80]

Azasteroid Inhibitors

The azasteroid series of inhibitors was first disclosed by Merck in the early 1980s.[81] Many of the original papers were published prior to the identification and characterization by Anderson and Russell of the human 5α-reductase isozymes,[82] and therefore potencies were quoted versus crude 5α-reductase from rat or human prostate homogenate.[83] In general, results quoted versus 5α-reductase from crude human prostate homogenate can be assumed to be versus the human 5α-R2 isozyme, while those quoted versus 5α-reductase isolated from human skin can be assumed to be versus the human 5α-R1 isozyme. The key 4-aza-3-oxo-5α-androstane pharmacophore and basic SAR are outlined in Figure 13. In general, the structural requirements for the inhibition of the crude human prostatic enzyme are more stringent than for the rat enzyme. A-Ring modifications to the 4-aza-3-oxo-5α-androstane template generally decrease potency, and compounds with $\Delta^{1,2}$ ($R_1 = CH_3$) and $\Delta^{5,6}$ unsaturation have slightly weaker potency versus human 5α-R. The $\Delta^{1,2}$ unsaturation has subsequently been shown to be important for good *in vivo* activity presumably due to the irreversible mechanism of inhibition which can result from NADPH dependent hydride transfer to the $\Delta^{1,2}$ bond of the A-ring Michael acceptor (see below).[84] The C17-substituent (*β*-preferred) can dramatically affect potency, and a great range of modifications to the C17-side chain has subsequently appeared in the patent literature although potencies for many compounds have not been reported.[85] *β*-C17-Amides of small lipophilic amines are preferred,

Table 8. SAR of 4-Substituted 3-Oxo-4-androstene-17β-carboxamides[a]



		IC_{50} (nM)	
no.	R	human 5α-R1 (transfected 293 cells)	human 5α-R2 (transfected SW-13 cells)
22	CN		2.9
23	SH	709	437
24	Cl	>1000	192
25	Br	981	387

[a] For assay conditions, see ref 86.

and simple esters and ketones are generally less active than their more lipophilic analogs. The combination of an optimal β-C17-substituent and an unsubstituted 4-position affords good potency and concomitant selectivity over androgen receptor binding ensuring a single mode of action.

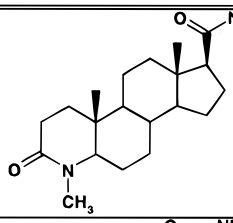
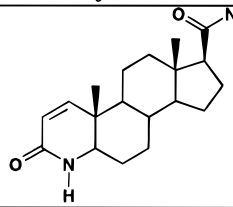
In summary, the steroidal pharmacophore provides an anchor between the key A-ring lactam and the C17-substituent. The former acts as a transition state mimic of the intermediate enolate **21**, whereas the latter significantly enhances potency *via* binding at a pocket largely lipophilic in character.

A recent paper by Singh highlights the key role of the A-ring lactam of the azasteroidal inhibitors for potent inhibition of the human 5α-R isozymes.[86] A range of 4-substituted 3-oxo-4-androstene-17β-carboxamides were prepared and compared with the corresponding 4-aza-steroidal inhibitors (Table 8). While the 4-cyano-substituted compounds are potent inhibitors of 5α-R2,[87] variations of the 4-substituent lead to significantly decreased activity. This series of compounds is also potent androgen receptor antagonists.

A program of work in Merck to exploit the 4-azasteroid series led to the discovery of potent inhibitors of human 5α-reductase with *in vivo* efficacy. 4-MA is a potent dual inhibitor of both human 5α-reductase isozymes which was halted in clinical development due to hepatic toxicity.[88] Other publications have also highlighted lack of selectivity over 3β-HSD (an important enzyme in the steroidal biosynthetic pathway) as an undesired property of 4-MA.[89] The Δ^1-unsaturated analog MK-906 (finasteride) has since been marketed for the treatment of BPH. This compound is a potent inhibitor of 5α-R2 with only weak *in vitro* activity versus the 5α-R1 isozyme (Table 9). At the clinical dose (5 mg/day) finasteride causes a 65−80% lowering of plasma DHT levels; residual DHT may arise from continued turnover of testosterone by the 5α-R1 isozyme which is not inhibited effectively at the clinical dose.[90] Generally, finasteride has shown moderate clinical efficacy in BPH patients (see later), and in a recent large study there was no significant overall improvement in symptoms.[91]

The hypothesis that a dual inhibitor of both isozymes would lead to a greater reduction of both plasma and prostatic DHT and therefore greater clinical efficacy was put forward by a number of investigators. Consequently, there has been a resurgence of interest in the azasteroid series, and SAR versus the two human 5α-reductase isozymes has now been more thoroughly explored. Variation of the C17-amide substituent on the optimal 4-aza-3-androstane skeleton has proven a particularly fruitful tactic in the search for potent dual azasteroid inhibitors.[92] For example, anilides show good potency versus both 5α-R1 and 5α-R2 (Table 10), whereas the introduction of an alkyl group at the anilide nitrogen substantially reduces potency versus both isozymes (compare **26** and **27**, Table 10). This alkyl group reduces the conformational preference for the *s-trans*-amide conformer which is assumed to be the binding conformation. The diphenyl amide **28** has a similarly weak affinity akin to **27** indicating the unfavorable nature of the *s-cis*-phenyl ring. The indolinyl amide **29**, which has a stronger preference for the *s-trans*-conformer, retains only 5α-R2 activity indicating that the 5α-R1 isozyme has stricter conformational requirements. The introduction of an *o*-CF_3 group to the anilide increases 5α-R1 potency (e.g., **30**), and the naphthyl or biphenyl analogs **31** and **32** indicate the presence of extended lipophilic interactions in this region which may be exploited to enhance 5αR-1 potency in the opti-

Table 9. 4-MA and MK-906[a]

Name/No	Structure	Rat 5α-R IC_{50} nM	Human 5α-R1 IC_{50}nM	Human 5α-R2 IC_{50}nM
4-MA		9.5	1.7	1.9
MK-906 (Finasteride)		20	410	9.4

[a] Data obtained using the screening protocol in ref 110.

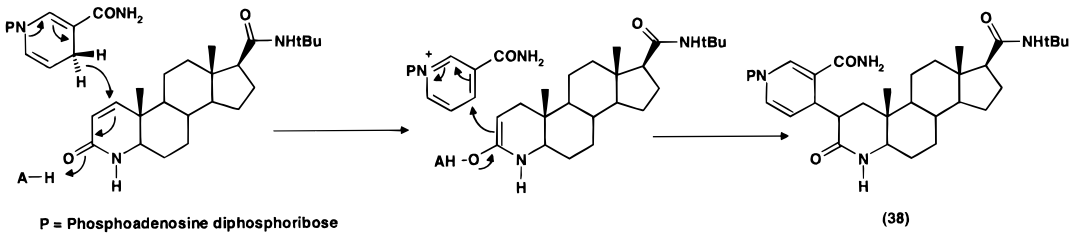
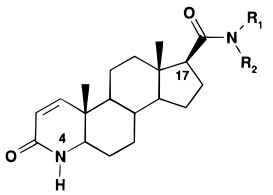


Figure 14.

Table 10. Variation of the C17-Amide Substituent on the Optimal 4-Aza-3-androstane Skeleton[a]



			IC$_{50}$ (nM)	
compd	R_1	R_2	human 5α-R1	human 5α-R2
26	Ph	H	20	<0.1
27	Ph	CH_3	350	0.2
28	Ph	Ph	>1000	25.2
29	1-indolinyl		120.2	0.4
30	2-$CF_3C_6H_4$	H	5.6	<0.1
31	3-$C_6H_5C_6H_4$	H	14.0	<0.1
32	1-naphthyl	H	8.1	0.2
GG745	2,5-CF_3-C_6H_3	H	2.4	0.5

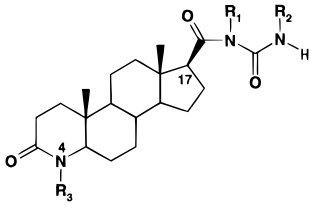
[a] Assay conditions as described in ref 115.

mal s-*trans*-amide conformer. Polar substituents (OH, NH_2) generally lead to a reduction in potency. GG745 (Table 10) is among the most potent dual inhibitors to emerge to date. It has irreversible kinetics versus both isozymes of human 5α-reductase and is 60-fold more potent than finasteride versus 5α-R1. Preliminary data in clinical trials of this compound indicate >90% reductions in DHT levels in man (40 mg single dose).[93]

Farmitalia Carlo Erba has subsequently published on a series of C17-acylurea-substituted 4-azasteroids exploiting the tolerance of functionality at this position (Table 11).[94] Significantly greater potency versus human 5α-R is obtained with a C4-methyl group and a saturated A-ring (compound **33**). Again, potency versus the two isozymes of human 5α-R has not been disclosed. One of the most potent analogs, turosteride, is a close analog of 4-MA but unlike 4-MA is devoid of binding at the rat androgen receptor and is a weak inhibitor of 3β-HSD (IC_{50} = 2.5 μM).[95] Turosteride reduces ventral prostate size in a rat model of BPH at 3 mg/kg/day orally indicating its potential use as a therapeutic agent.[94]

The $\Delta^{1,2}$ azasteroid compounds of the finasteride class were initially thought to act as transition state mimics whereby the conformation of the A-ring lactam closely mimics that of the enol form of the transition state of 5α-reduced testosterone (Figure 11). However, recent work by both Glaxo[96] and Merck[84] indicates that finasteride and close analogs are slow offset, essentially irreversible inhibitors. The most likely cause of the slow offset inhibition is alkylation of the enolate formed on 1,4-reduction of the Δ^1 A-ring of the finasteride skeleton (Figure 14). Indeed, Merck has demonstrated the presence of **38** in the inhibited form of 5α-R1.[84] This observation concurs with the surprisingly good *in vivo* activity of finasteride and other $\Delta^{1,2}$-unsaturated aza-

Table 11. C17-Acylurea-Substituted 4-Azasteroids[a]



					human prostatic 5α-R IC$_{50}$ (nM)
compd	unsaturation	R_1	R_2	R_3	(5α-R2)
33		C_6H_{11}	C_6H_{11}	CH_3	41
34		tBu	tBu	CH_3	212
turosteride		iPr	iPr	CH_3	55
35		iPr	iPr	H	381
36	$\Delta^{1,2}$	iPr	iPr	CH_3	1218
37	$\Delta^{1,2}$	iPr	iPr	H	1553

[a] For assay conditions, see ref 94.

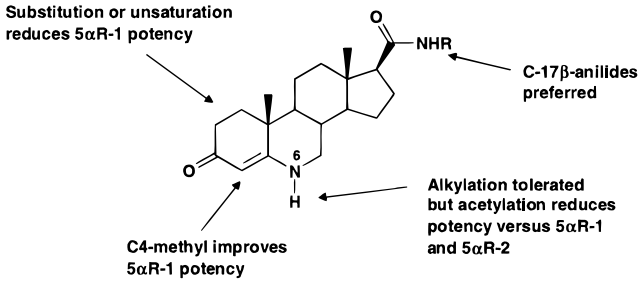


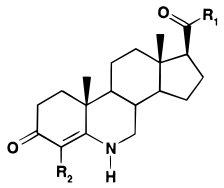
Figure 15.

steroids where irreversible inactivation of 5α-R leads to a longer pharmacodynamic effect than would be predicted from the pharmacokinetic profile.

Glaxo has reported a series of 6-azaandrost-4-en-3-one inhibitors of 5α-reductase where the ketoenamine functionality mimics the transition state for NADPH dependent hydride addition to the Δ^4 alkene of testosterone.[97] This series differs from the 4-azasteroids in that the kinetics of inhibition versus human 5α-R1 and 5α-R2 are not consistent with irreversible enzyme inhibition but with slow offset inhibition. The higher reduction potential of a ketoenamine compared to that of an α,β-unsaturated ketone presumably prevents these compounds from acting as substrates for 5α-R. In common with the SAR of the 4-azasteroids, good *in vitro* potency versus 5α-R1 is more elusive than for the 5α-R2 isozyme. The more general *in vitro* SAR features of the 6-azasteroidal skeleton are summarized in Figure 15. Of particular note is the increased potency versus 5α-R1 on the introduction of small lipophilic groups at C4 (as observed for the 4-azasteroids), whereas alteration of the C1- or C2-position (e.g., *via* substitution or unsaturation) is deleterious to 5α-R1 potency.

This series has, however, provided some exceptionally potent inhibitors of human 5α-R2 (Table 12). By careful

Table 12. 6-Azaandrost-4-en-3-one Inhibitors of 5α-Reductase[a]

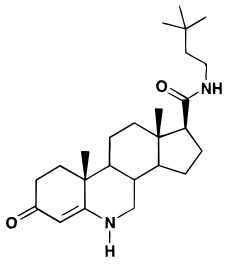


compd	R_1	R_2	human 5α-R1 K_i (nM)	human 5α-R2 IC_{50} (nM)	3β-HSD K_i (nM)
finasteride			150	0.18	11000
39	OCH_3	H	150	3.2	12
40	*O*-2-adamantyl	H	6.9	<0.1	180
41	morpholine	H	2200	7.1	190
42	$NHCH(4\text{-}ClPh)_2$	H	20	0.12	510
43	$NHCHPh_2$	H	30	<0.1	150
44	NHPh	H	240	1.4	10
45	$2\text{-}tBu\text{-}5\text{-}CF_3\text{-}C_6H_3NH$	H	8.8	<0.1	1600
46	$3,5\text{-}di\text{-}tBu\text{-}C_6H_3NH$	H	8.0	<0.1	7.8
47	$2,5\text{-}CF_3\text{-}C_6H_3NH$	CH_3	0.2	<0.1	19
48	$2,5\text{-}CF_3\text{-}C_6H_3NH$	Cl	0.2	<0.1	190
49	*N*-[1-(4-chlorophenyl)cyclopentyl]	CH_3	0.3	<0.1	160
50	*N*-[1-(4-chlorophenyl)cyclopentyl]	Cl	0.6	<0.1	490

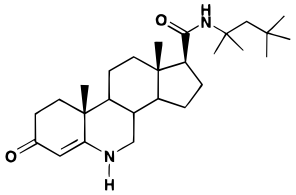
[a] For assay conditions, see refs 97 and 98.

optimization of the C17-substituent, potent dual inhibitors of both isozymes of 5α-reductase were obtained. In particular, lipophilic substitution at C17 appears optimal (see **43**). Compound **43** demonstrated efficacy equivalent to finasteride in a castrated rat model of DHT dependent prostate growth[97] and had 79% oral bioavailablity ($T_{1/2} = 4.8$ h) in the dog. Selectivity over 3β-HSD was achieved by further optimization of the C17-substituent (Table 12). Comparison of compounds **44** and **45** (Table 12) indicates the sensitivity of both 5α-R1 and 3β-HSD to the C17-substituent. In general, 5α-R1 prefers large lipophilic groups at C17, whereas 3β-HSD prefers small and/or lipophilic groups (compare **44** and **46**, Table 12). The substitution pattern on the aniline and on the A-ring is also important, however, since moving from 3,5-disubstituted anilides (**46**) to 2,5-disubstitution with a 4-Cl in the A-ring (**48**) significantly increases selectivity over 3β-HSD. Compound **45** also demonstrated activity equivalent to finasteride in the castrated rat model of DHT dependent prostate gowth[98] and had 67% oral bioavailablity ($T_{1/2} = 8.8$ h) in the dog. Incorporation of the optimal A-ring substitution pattern with the best C17-β-substituent led to very potent dual inhibitors (e.g., **49** and **50**) of both 5α-R isozymes with good oral activity and up to 1000-fold selectivity over 3β-HSD.[98]

In an elegent study of conformationally restricted C17-substituents, the Glaxo team was able to develop a predictive model for potency versus 3β-HSD.[98] Compounds **51** and **52** were key to the analysis since molecular modeling studies predicted significantly different preferred minimum conformations about the C17-amide. The lower potency of **52** versus 3β-HSD was rationalized by assuming that it is poorly accepted into the enzyme in its preferred *s-cis* conformation and therefore any C17-substituent which is capable of adopting a similar conformation will confer selectivity over 3β-HSD but retain potency versus 5α-R1 and 5α-R2 (Figure 16).



(**51**)
3βHSD IC_{50} = 8.3nM



(**52**)
3βHSD IC_{50} = 150nM

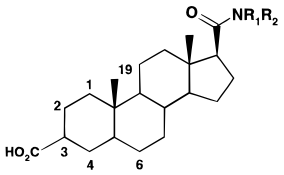
Figure 16.

Steroidal Carboxylic Acid Inhibitors

The androstenecarboxylic acids were designed as mimics of the enolate intermediate **21** (Figure 11) where the anionic carboxylate ion serves as a mimic for the enolate oxygen in binding to the active site. The initial SAR versus crude human 5α-R homogenate indicated the need for Δ^3 unsaturation in the A-ring and the beneficial effect of additional Δ^5 unsaturation. There was strong evidence for an unfavorable steric interaction on substitution at C6, and removal of the C19-methyl group was deleterious. The SAR of the C17-substituent was similar to that found in the azasteroidal inhibitors with the diisopropyl (**53**) and pivalyl (**54**) amides proving optimal (Table 13).[99] One agent from this class (epristeride) has entered clinical trials for the treatment of BPH.[100] Although selective over 3β-HSD and potent versus 5α-R2 ($K_i = 0.18$ nM), the compound is weak versus 5α-R1. Clinically it reduces DHT to a lesser extent than finasteride (25% at 0.4 mg and 54% at 160 mg) and is unlikely to give greater clinical benefit.[101]

Similar SAR trends were noted for the estratrienecarboxylic acids containing an aromatic A-ring.[102] Several subsequent papers have appeared on the SAR of carboxylic acid isosteres. In particular, the nitro derivatives **63**−**65** show interesting SAR with respect to their acid analogs **60**−**62** (Table 14).[103] Although the nitro group may be considered isosteric with a carboxylate anion, it is uncharged at physiological pH unlike the carboxylate. Compound **63** proved to be a potent *in vitro* inhibitor of human 5α-R (crude prostatic preparation); compounds **64** and **65** were significantly weaker. Compound **63** demonstrated competitive inhibition kinetics versus testosterone suggesting that the

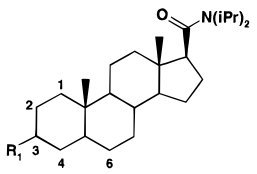
Table 13. Steroidal Carboxylic Acid Inhibitors[a]



compd	NR_1R_2	substituent	unsaturation	5α-R IC_{50} (nM) human	5α-R IC_{50} (nM) rat
53	$N(iPr)_2$		3−4	30	70
54	NHtBu		3−4	110	11
epristeride	$N(iPr)_2$		3−4, 5−6	7−18	35−50
55	$N(iPr)_2$		2−3, 4−5, 6−7	7−12	300
56	$N(iPr)_2$		2−3, 4−5, 11−12	7	47
57	$N(iPr)_2$	4-F	3−4	26	35
58	$N(iPr)_2$	4-CH_3	3−4, 5−6	35	70
59	1-naphthyl	6-CH_3	3−4, 5−6	170	200

[a] For assay conditions, see ref 99.

Table 14. SAR Trends for the Estratrienecarboxylic Acids[a]



no.	R_1	unsaturation	$K_{i(app)}$ (nM) human	$K_{i(app)}$ (nM) rat
60	HO_2C	3−4	30	70
61	HO_2C	3−4, 5−6	7	35
62	HO_2C	A-ring aromatic	20	356
63	O_2N	3−4	50	inactive
64	O_2N	3−4, 5−6	590	inactive
65	O_2N	A-ring aromatic	>5000	inactive
66	HO_3S	A-ring aromatic	20	1700
67	HO_3P	3−4, 5−6	25	200
68	HO_2P	3−4, 5−6	7	160
69	$HOCH_2$	3−4, 5−6	4200	5300

[a] For assay conditions, see ref 105.

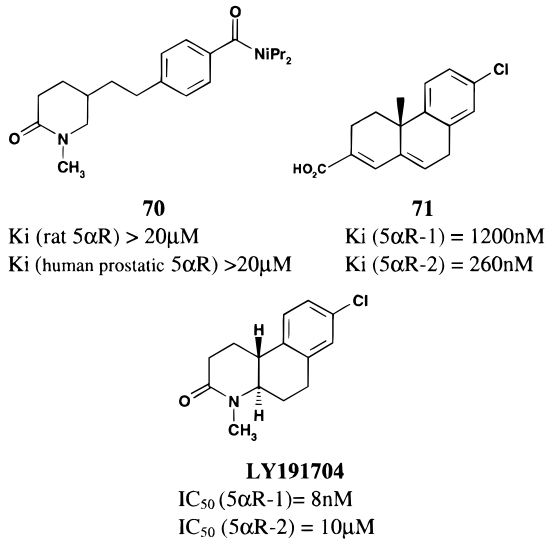


Figure 17.

neutral nitro compound binds to the E−NADPH complex while the charged carboxylates display uncompetitive kinetics and bind to the E−$NADP^+$ complex. Interestingly none of the nitro compounds showed significant inhibition of rat 5α-R at micromolar concentrations. The sulfonic acid **66**,[104] phosphinic acid **67**, and phosphonic acid **68**[105] also proved potent inhibitors of human 5α-R, although like the nitro compounds they performed poorly versus the rat enzyme. The requirement for the C3-functionality to provide a negative charge at physiological pH in this series is reinforced by the weak activity of the alcohol **69** versus both rat and human enzyme preparations. The function of the C3-moiety is presumably to act as an H-bond acceptor from a residue in the enzyme which would normally donate a hydrogen bond to stabilize the enolate **21** in Figure 11. That negatively charged groups (CO_2^-) or isosteres of the carboxylate (NO_2) best mimic this interaction indicates that a pK_a-matched H-bond with a Lys or Arg donor may be operative. In addition, an interaction between the negatively charged C3-moiety and the positively charged $NADP^+$ cofactor after the enzyme has turned over substrate (see Figure 12) is possible, especially if the cofactor lies directly under the A-ring of the steroidal skeleton in the transition state and mimics thereof.

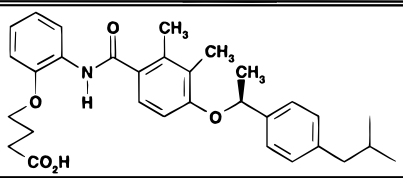
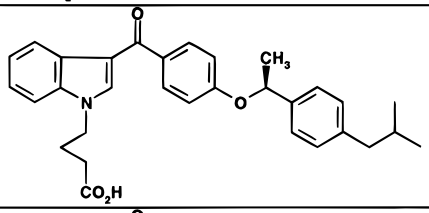
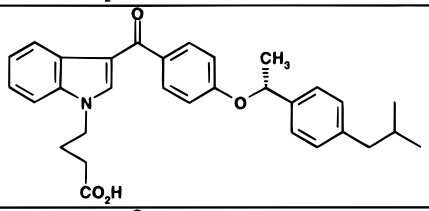
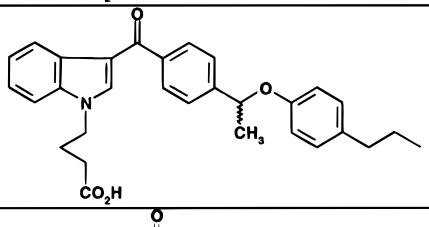
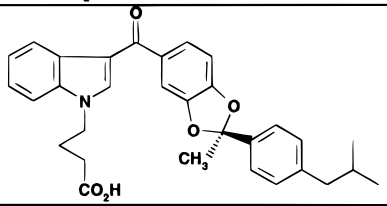
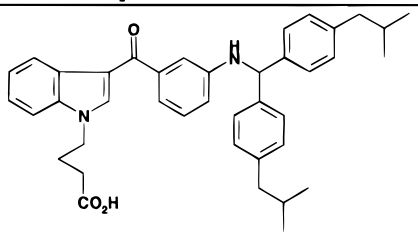
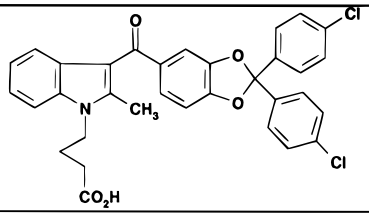
Incorporation of a C17β-substituent optimized for both isozymes of 5α-R (see the 4-azasteroid and 6-azasteroid classes above) into the epristeride skeleton leads to potent dual inhibitors.[98] However, there are currently no reports of the clinical effects of these compounds.

Nonsteroidal Inhibitors

A number of classes of nonsteroidal inhibitors of 5α-reductase have now been identified. In general, these have emerged from (a) the design of nonsteroidal mimics of the azasteroid inhibitors, e.g., finasteride, (b) an early nonsteroidal lead (ONO-3805, Table 15) prepared as a leukotriene synthesis inhibitor,[106] or (c) high throughput screening. Many of these inhibitor classes display interesting selectivity profiles versus the two human 5α-R isozymes.

Nonsteroidal mimics of the tetracyclic skeleton of the azasteroids include the pyridones (e.g., **70**) where the B- and C-rings of the steroid system have been replaced by an acyclic linker (Figure 17).[107] These compounds display relatively weak activity versus both the rat and human isozymes. Their poor potency does, however, illustrate the need for both A- and B-rings to be present with the correct fusion pattern for good recognition at the enzyme active site. No potent inhibitors have been published with only an A-ring mimic of the azasteroidal

Table 15. Nonsteroidal Inhibitors of 5α-Reductase[a]

Name\ No	Structure	Rat 5α-R IC_{50}nM	Human 5α-R1 IC_{50}nM	Human 5α-R2 IC_{50}nM
ONO3805		1.7	-	256
(72)		1	40	4
(73)		30	574	69
(74)		5	8	10
(75)		9	25	23
FK143		128	38	36
(76)		588	10	6,300

[a] For assay conditions, see ref 110.

template. Two teams have focused on series where the D-ring of the steroidal inhibitors is replaced. Removal of the D-ring from the steroidal carboxylates gave the weak epristeride analog **71** with some selectivity for 5α-R2.[108] Removal of the D-ring from the azasteroidal class gave the inhibitor LY191704 which displays good selectivity for 5α-R1.[109]

The nonsteroidal *o*-hydroxyaniline ONO-3805[106] (Table 15) proved a weak lead *in vitro* versus human 5α-R2. Subsequent followup by workers at Fujisawa and Pfizer has led to the discovery of more potent analogs. Workers at Pfizer prepared the C3-acylindole **72** which demonstrated improved, balanced potency versus both 5α-reductase isozymes (Table 15).[110] The α-methylbenzyl chiral center was essential for good *in vitro* potency with the *S*-enantiomer significantly more potent than its antipode (**73**). Compound **72** exhibited a long half-life and good oral bioavailability and was progressed to a rat *in vivo* model of DHT dependent prostate growth where it demonstrated a 35% reduction in prostate

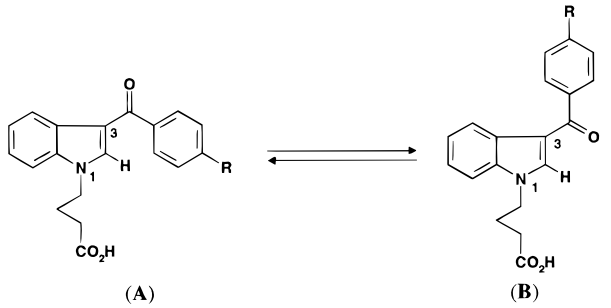


Figure 18.

weight after 10 days (1 mg/kg po). Reversal of the ether linkage (**74**, Table 15) gave a compound of equivalent overall conformation and potency indicating that the ether link provided a conformational preference rather than a specific binding motif. The benzodioxolane **75** adopts a similar minimum conformation to the ether **72** and proved a potent dual inhibitor of both 5α-R isozymes.[110]

FK-143[111] has been disclosed by workers at Fujisawa as a dual inhibitor of both human 5α-R isozymes (Table 15). This compound is structurally similar to the Pfizer series above and shows similar suppression of plasma DHT levels in the rat and dog *in vivo* and marked reduction of rat prostate growth in an androgen dependent rat model.[112]

In common with the steroidal carboxylic acid inhibitors, these compounds require the carboxylic acid moiety for potency and the 3-acylindole motif is crucial for dual activity presumably by allowing access to both the conformations A and B (Figure 18). The corresponding 2-methyl analog **76** which adopts conformation B is a selective inhibitor of 5α-R1. Fine tuning of the potency in this 5α-R1-selective series was achieved by modification of the benzodioxolane substituents, with those shown in structure **76** optimal (Table 15).[113]

Screening of aryl carboxylates versus the human 5α-R isozymes by SKB led to the discovery of two series of nonsteroidal inhibitors based on a benzophenone or indolecarboxylic acid skeleton.[114] The SAR of both series versus human 5α-R2 is summarized in Figure 19. In the benzophenone series the linker between the A- and B-rings proved crucial, whereas the linker between the B- and C-rings was more tolerant of variation. Both the A-ring carboxylic acid and the C-ring are critical since benzophenone carboxylic acid is a weak inhibitor (K_i = 840 nM). Compound **77** has uncompetitive kinetics versus 5α-R2 characteristic of the steroidal carboxylic acids discussed above. In the indole series there was a strong preference for substitution at the 5- or 6-position of the indole ring.

5α-Reductase 1-Selective Compounds

The presence of the 5α-R1 isozyme in the scalp and skin coupled with the potential involvement of this isozyme in the development of acne, hirsuitism, and male pattern baldness has prompted some of the major pharmaceutical companies to pursue the SAR toward highly selective 5α-R1 inhibitors. For example, workers at Pfizer have prepared a series of nonsteroidal 5α-R1 inhibitors exemplified by compound **76** (Table 15). These compounds are selective for 5α-R1 by virtue of the 2-methyl substituent on the indole ring which locks the conformation about the 3-acylindole moiety.[113]

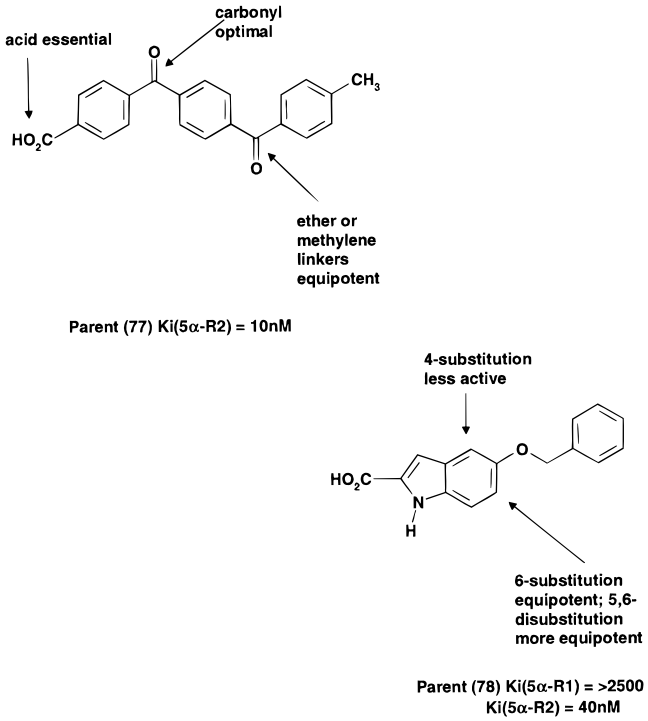
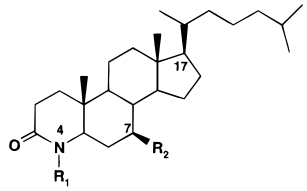


Figure 19.

Table 16. MK-386 and Analogs[a]



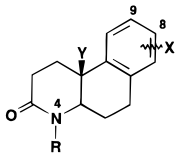
				IC_{50} (nM)	
compd	R_1	R_2	Δ	human 5α-R1	human 5α-R2
79	H	H	Δ^5	19.1	ND
80	CH_3	H		1.7	218
MK-386	CH_3	CH_3		0.9	154
81	Et	CH_3		3.3	1390
82	CH_3	Ph		134	428

[a] For assay conditions, see ref 115.

Merck identified the 4-aza-4-methylcholestan-3-one skeleton **79** as a 100-fold selective inhibitor of 5α-R1 (Table 16). The introduction of a 4- and a 7β-substituent increased potency and, in some cases, selectivity for 5α-R1 (compare **79** with **80**, MK-386, and **81**, Table 16). However, increasing bulk of this substituent was deleterious with 7β-phenyl significantly less active (**82**). The binding at 5α-R1 is, therefore, enhanced by a small hydrophobic substituent at the N4-position. Unsaturation at Δ^1 or Δ^5 of the cholestanone skeleton had little effect on potency or selectivity.[115] MK-386 has been progressed to human clinical trials for the treatment of acne, baldness, and female hirsuitism. In addition, it is currently under investigation in combination with finasteride for the treatment of BPH. Interestingly the incorporation of the cholestanone 17-substituent into the Glaxo series of 6-azasteroids did not give rise to significant selectivity for 5α-R1 over 5α-R2.[116]

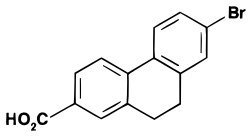
Lilly has published a series of tricyclic nonsteroidal benzoquinone 5α-R1-selective inhibitors.[109] The parent benzoquinolinone **83** is a weak inhibitor (IC_{50} = 6 μM). However, potency was increased *via* the introduction of

Table 17. Nonsteroidal Benzoquinone 5α-R1-Selective Inhibitors[a]



compd	R	X	Y or $\Delta^{4a,10a}$ unsaturation	IC_{50} (nM) human 5α-R1	IC_{50} (nM) human 5α-R2
83	H	H	$\Delta^{4a,10a}$	6500	
84	H	8-Cl	$\Delta^{4a,10a}$	460	
85	CH_3	8-Cl	$\Delta^{4a,10a}$	30	
LY191704	CH_3	8-Cl	H *trans*-fused ring junction	8	10 μM
86	CH_3	8-Cl	Me	17	

[a] For assay conditions, see ref 109.



(**87**)
Ki (5α-R1) = 26nM
Ki (5α-R2)= 10μM

Figure 20.

substituents in the aromatic ring (see **84**) and the introduction of a small hydrophobic group at N4 analogous to the SAR of the steroidal 5α-R1-selective Merck inhibitors above. The octahydro derivatives were typically more potent with the *trans*-isomers more active than the *cis* (Table 17). LY191704 which has the optimal skeleton and an 8-Cl substituent has been progressed to human clinical trials; it is a weak inhibitor of 5α-reductase activity in human prostate homogenates (IC_{50} > 10 μM); the compound is also a weak inhibitor of the rat enzyme.[117] Combination of the Lilly tricyclic inhibitor series with the Glaxo 6-azasteroid series to generate tricyclic phenanthridin-3-ones led to relatively weak 5α-R1 inhibitors.[118]

The tricyclic nonsteroidal aryl acid **87** is also selective for 5α-R1 (Figure 20).[119] This compound is a tricyclic analog of the steroidal aryl acid series of 5α-R2-selective compounds (see above). These tricyclic aryl acids can also be compared with the nonsteroidal aryl acids discussed above (Figure 19). It can be concluded from this comparison that inhibiton of 5α-R1 in the aryl carboxylic acid series requires a good six-membered B-ring mimic in addition to the A-ring transition state mimic. However, incorporation of a mimic for the C17β-substituent of the steroidal pharmacophore is not essential for 5α-R1 potency.

Clinical Studies in BPH

The efficacy of selective α_1 adrenoceptor antagonists in the treatment of BPH has been well established and first reported by Hedlund et al.[120] using prazosin. Subsequently, at least 35 placebo-controlled clinical trials have been conducted using α_1 adrenoceptor antagonists, and rigorous analysis of all published clinical trials on α_1 adrenoceptor antagonists in BPH has recently been reviewed by Eri and Tveter,[121] involving meta-analysis of 29 studies and almost 1500 patients. At effective doses, mean maximum flow rate was increased by 2 mL/s (range 1.4−3.9), although this could be influenced by the predose baseline value. Symptom score on average was improved by 14% (range 10−39), although there was not a definite causal relationship between increases in flow rate and symptom score. Whether these increases in flow rate represent a ceiling on efficacy is difficult to assess since studies have generally used maximally tolerated doses, with a low incidence of side effects, although in some studies a clear dose-related improvement in urodynamics has been shown. As already discussed, currently available agents (doxazosin, prazosin, terazosin, and alfuzosin) show little or no α_1 subtype selectivity *in vitro* or prostate selectivity *in vivo* which is entirely consistent with the overall clinical profile of these agents where, by and large, only pharmacokinetic differences are observed. In some recent studies, the clinical profile of tamsulosin has been described. While this compound is clearly a potent antagonist at prostatic α_1 adrenoceptors *in vitro*, having selectivity over the α_{1b} subtype, in clinical studies only modest improvements in either peak urinary flow, mean urinary flow, or symptom score have been observed with this compound, and on this basis, tamsulosin cannot be differentiated from other nonselective agents. While the profile of prostate-selective agents needs to be established in the clinic, it is interesting to note that in one reported clinical study,[122] relatively high doses of indoramin (100 mg) resulted in much greater improvements in urinary flow (~9 mL/s) than seen with nonselective α_1 adrenoceptor antagonists, suggesting that selective antagonism of the prostatic α_1 adrenoceptor may lead to greater relief of outlet obstruction. It is generally accepted that α_1 adrenoceptor antagonists are highly effective in attenuating the symptoms of BPH, often with only modest improvements in urinary flow, and the extent of symptom improvement is generally greater than with other classes of drug such as 5α-reductase inhibitors.

The clinical effects of finasteride have been the subject of several recent reviews.[123−125] In summary, finasteride causes a reduction in prostate volume by a mean of approximately 19%, with the greatest fall occurring during the first 3−6 months of treatment. Finasteride causes involution of prostatic glandular epithelium, with lesser effects on the fibromuscular stroma,[126] and it may therefore be most effective in patients with large prostates having a high epithelial component. The reduction in prostate volume is accompanied by modest improvements in urinary flow rates and symptom score. In a well-designed study of 2-years duration involving 707 patients,[127] finasteride significantly increased peak urinary flow rates by a mean of 1.5 mL/s relative to a decrease of 0.3 mL/s in the placebo group, the symptom score for the finasteride group was 2.2 points lower than for placebo, and prostate volume decreased by 19% while that for the placebo group increased 11%. These data support the conclusion that finasteride can reverse the natural progression of BPH.[127] Nevertheless, the improvements in peak flow and symptom score are generally at the lower end of the range reported for α_1 adrenoceptor antagonists[121] and have not been maintained in all clinical trials. In a recent large study involving 1229 men with BPH, Lepor and colleagues[91] directly compared the effects of terazosin and finasteride

on flow rate and symptom score over 1 year. In comparison to placebo, finasteride did not change either symptom scores or peak flow rate. In contrast, terazosin improved symptom scores by 6.1 points (2.6 for placebo, from a baseline score of 16) and peak flow rate by 2.7 mL/s. A key finding from this study was that the effect of both drugs given in combination was no better than terazosin alone. These data clearly show the superior profile of α_1 blockers in terms of symptomatic and urodymamic improvement and, when compared to findings in other trials, suggests that finasteride may only be effective in patients with large prostate glands. Overall, these findings are likely to lead to the widespread use of α_1 blockers in the treatment of patients with mild to moderate symptoms. With the emergence of highly prostate-selective α_1 antagonists,[128] a key issue will be to determine if these agents provide additional urodynamic improvement since the extent to which intraurethral pressure is decreased with currently used α_1 antagonists is not clear (for example, in relation to complete sympathetic blockade achieved by spinal anesthesia[6]). Whether any urodyamic improvement is accompanied by additional symptomatic improvement also remains to be established.

Hormonal and Growth Factor Regulation of Prostate Growth: Androgen Withdrawal, Estrogen Withdrawal, and Growth Factors

Androgen Withdrawal. As introduced earlier, the first approach to reducing the symptoms of BPH through reduction in size of the enlarged gland involved surgical castration. Androgen (testosterone and DHT) withdrawal through the use of pharmacological agents, leuteinizing hormone-releasing hormone (LHRH) agonists, and androgen receptor antagonists has continued to be investigated in relation to BPH. LHRH agonists are generally structural peptide mimics of the native hormone. They cause a desensitization of the LHRH receptor complex in the pituitary resulting in greatly reduced release of leuteinizing hormone (LH) which normally functions to stimulate the Leydig cells of the testes to produce androgens.[21] As a consequence circulating levels of androgens are reduced to castrate levels, and intraprostatic testosterone and DHT are both reduced, 90% and 75%, respectively.[21] In this respect the effects of LHRH agonists differ from the 5α-reductase inhibitor finasteride, which reduces DHT to a similar or greater extent but elevates testosterone to approximately 8-fold that in the untreated prostate.[9] It appears that the elevated prostatic testosterone during finasteride treatment may partially compensate for the low level of DHT, since prostate specific antigen (PSA), a marker of prostate epithelial cell function, is less effectively suppressed with finasteride.[123] A recent review of the literature data for LHRH agonist-induced prostate involution (five studies), although admittedly limited by the relative lack of recent double-blind placebo-controlled trials, would suggest that chemical castration results in greater shrinkage of the prostate than that achieved with finasteride (mean 37.5% vs 19%).[129] In addition, it is apparent from studies in the rat that androgen withdrawal through surgical castration has a more profound effect on prostate cell apoptosis than 5α-reductase inhibition.[130,131] Studies in man with LHRH agonists have, however, been too small to determine whether this apparently greater gland shrinkage results in better urodynamic or subjective symptom improvement.[129] Despite the evidence that LHRH agonists may give greater prostate shrinkage than finasteride, they have not achieved widespread use in BPH due to their high cost and the side effects associated with testicular androgen withdrawal, specifically, loss of libido, impotence, hot flushes, and risk of bone demineralization on long-term use.[11] Recently, a peptide LHRH antagonist, cetrorelix (*N*-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N^5-(aminocarbonyl)-D-ornithyl-L-leucyl-L-arginyl-L-prolyl-D-alaninamide), has been investigated in BPH patients where it appears to have a similar effect on the prostate to the LHRH agonists: mean 44% reduction.[132] Cetrorelix has the theoretical advantage over LHRH agonists in that it does not cause the initial surge in testosterone levels resulting from hyperstimulation of LH and testosterone production prior to desensitization of the pituitary.

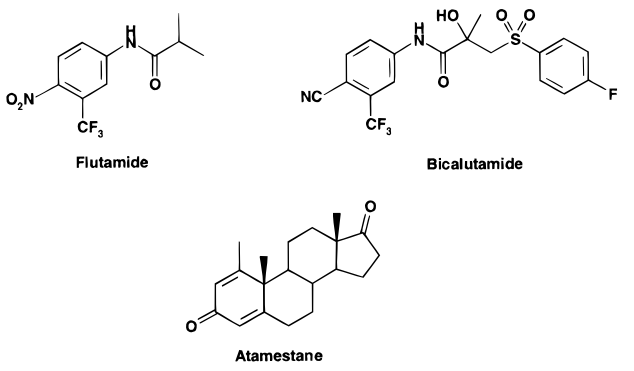


Figure 21.

The second approach to androgen withdrawal has involved specifically targeting the androgen receptor with receptor antagonists. Two agents have been most widely investigated in BPH: flutamide and bicalutamide (Casodex) which are both nonsteroidal (Figure 21). Prostate shrinkage is comparable to that of finasteride, e.g., 26% for Casodex in a recent study.[133] Although the incidence of reduced libido and impotence appears more modest than with LHRH agonists, gynecomastia is common (>50%). Consequently it appears unlikely that androgen receptor antagonists will displace finasteride from its lead in the prostate shrinker class. They do, however, have important roles in the palliative treatment of prostatic cancer, as sole agents and in combination with LHRH agonists to achieve complete androgen withdrawal by blocking the effects of adrenal androgens.

Estrogen Withdrawal. The role of estrogens in prostate growth is less well defined than that of androgens. The ratio of estrogen/androgen in plasma increases with aging, and the estrogen receptor is present in the human prostate where it is localized predominantly in stromal cells.[10] Since, on average, the stromal compartment of BPH tissue is increased more than the epithelium, it has been proposed that estrogens may be implicated in the development of BPH and that estrogen withdrawal could be efficacious in its treatment.[10] Two approaches to estrogen withdrawal may be considered, firstly inhibition of the aromatase enzyme which converts aromatizable androgens to estrogens and secondly blockade of the estrogen receptor with specific antagonists. The only in-depth investigation of the effects of estrogen withdrawal in BPH has been carried

out with the steroidal aromatase inhibitor atamestane which progressed to large phase II trials. The outcome of these studies, namely, lack of effect on symptoms and on prostate volume,[134] was disappointing and would at first sight appear to have disproven a role for estrogens in BPH. Closer evaluation of the data indicates that plasma levels of the estrogens, estradiol and estrone, were reduced only 40% and 60%, respectively, while in an earlier study the fall in intraprostatic estrogens was minimal.[135] Furthermore, plasma testosterone and dihydrotestosterone were increased 30−40% (due to inhibition of the negative feedback action of estrogen on the hypothalamic−pituitary axis), which may have stimulated proliferation of the epithelial tissue.[11] It therefore still remains to be proven whether estrogen withdrawal in BPH has value either as monotherapy or in combination with an androgen withdrawal approach, for example, 5α-reductase inhibition, to counteract the effect of elevated androgens on the prostate epithelium.

Endothelin Antagonists

The possibility that endothelin antagonists may have a therapeutic utility in the treatment of BPH is suggested by several pieces of experimental evidence. In human prostate, the presence of ET-1 has been confirmed, with ET-1 immunoreactivity localized to glandular epithelium.[136] In primary culture, prostatic epithelial cells secrete high levels of ET-1 at a rate 10-fold higher than observed with stromal cells. *In vitro*, ET-1 potently contracts isolated preparations of human prostatic smooth muscle through a calcium dependent, dihydropyridine insensitive mechanism, and the response is insensitive to the effects of α_1 adrenoceptor antagonists.[136] Thus far, two ET subtypes have been identified, and in human prostate, both ET_A and ET_B receptors can be demonstrated on the basis of ET-1 binding to prostatic membrane homogenates in which ET_A receptors predominate.[137] Quantitative receptor autoradiography by Kobayshi et al.[138] has shown that the ratio of ET_A and ET_B receptors is 2:1, and they are preferentially distributed in the stroma and epithelium, respectively. *In vitro*, the ET_A antagonist PD 155,080 blocks ET-1-mediated contractions of human prostate with a pA_2 of 7.0. However, since the ET_B agonist S6C causes contractions which are insensitive to the inhibitory effects of PD 155,080, a functional role for both ET_A and ET_B receptors has been suggested. Taken together, a functional role for both ET_A and ET_B subtypes can be shown.[137,139] *In vivo*, using the anesthetized dog, exogenous ET-1 causes a rise in prostatic intraurethral pressure and is blocked by PD 155,080. Thus, *in vitro* and *in vivo* data, together with the endogenous identification of this peptide, suggest that ET antagonists may have a role in attenuating prostatic tone. In addition, it has been shown that the level of ET-1 secreted by epithelial cells in culture is sufficient to induce mitogenic signaling in stromal cells.[140] Thus, factors which disrupt normal epithelial/stromal homeostasis in the prostate may allow a role for ET-1 in the pathogenesis of BPH, although which subtypes are involved in this response is currently unclear. The emergence of selective antagonists for ET receptors may ultimately offer an additional therapeutic option in the treatment of BPH.

Growth Factors

The endocrine effects of androgens and estrogens on the prostate gland are intimately linked to the paracrine and autocrine interactions between stromal and epithelial cells mediated by peptide growth factors.[141] Many growth factors and their receptors have been detected in the stromal and epithelial tissues of the prostate (for recent reviews, see refs 142 and 143). In particular, bFGF, EGF, KGF, and IGF-I/IGF-II have been shown to be mitogenic for prostate epithelial and/or stromal cells in culture.[142,143] There is a highly complex IGF system in the prostate consisting of IGF-I and IGF-II growth factors, IGF-I receptor, several binding proteins, and proteases suggesting that it occupies a key role in prostate growth and/or function.[144] Recently, it has been reported that there are changes in expression of components of the IGF system in fibroblasts cultured from BPH tissue vs normal prostate and these alterations, the first reported for any growth factor system in the prostate, may be involved in the development of BPH.[144] Overexpression of a bFGF-like gene in transgenic mice causes a dramatic increase in prostate volume,[145] while injection of EGF or bFGF directly into the rat prostate causes approximately 40% enlargement.[146] It is, however, by no means clear how these effects relate to the function and growth of the normal prostate, let alone the development of BPH in man. The relative heirarchy of the various growth factors in controlling prostatic growth and function *in vivo* has still to be determined. Nevertheless, it appears likely that improved understanding of the role of growth factors in the prostate, supported by the powerful molecular tools of transgenics and antisense, will lead to the next generation of medicinal approaches to BPH and prostate cancer. The ubiquitous tissue distribution of many growth factors and their key roles in intercellular communication and in the function and maintenance of cells will make selective targeting of the prostate a difficult challenge.

Summary

Significant advances have been made in the understanding of the physiology, pharmacology, and control of prostate growth. Androgen modulation has proved, thus far, to be of limited effectiveness in terms of symptomatic and urodynamic improvement. In this context, 5α-reductase inhibitors may not have a major long-term impact, especially when α_1 antagonists appear to be much more effective, particularly with regard to subjective symptomatic improvements. Whether prostate-selective α_1 adrenoceptor antagonists confer greater urodynamic improvement should become clear in the near future and as such could represent an attractive therapeutic option. A clear challenge for future therapies will be to elucidate those mechanisms/pathways which are pivotal in the development and progression of BPH and which offer the potential for pharmacological intervention. Modulation of potential mitogens in the prostate may represent a way forward, and while specificity remains a key issue, both endothelin antagonism and modulation of the key growth factors axis represent attractive mechanistic approaches.

Biographies

Barry Kenny received a B.Sc. (Honors) in pharmacology from the University of Sunderland in 1984. He worked for Syntex Research in Edinburgh (1984−1992) and during the

latter part of this employment completed a Ph.D. in-house (1989−1991) examining the properties of calcium channel antagonists *in vitro* and their effects in models of cerebral ischemia, carried out in conjunction with Prof. S. Nahorski (University of Liecester). He joined Pfizer Central Research in 1992, where he is currently a Senior Principal Scientist in the Discovery Biology Department.

David N. A. Fox graduated from the University of Cambridge, England, in 1987, with a B.A. (Honors) in chemistry. He received his Ph.D. from the University of Bath, England, working with Dr. T. C. Gallagher on an enantioselective synthesis of pumiliotoxin-251D. Between 1991 and 1993, he was a Royal Society European Science Exchange Fellow in the group of Prof. M. T. Reetz at the Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr, Germany, investigating chiral iron-based catalysts for enantioselective carbon−carbon bond formation. He joined Pfizer Central Research in 1993, where he is currently a Senior Scientist in the Discovery Chemistry Department.

Julian Blagg received a B.A. in chemistry from the University of Oxford in 1984. He subsequently completed a Ph.D. on the applications of organometallic chemistry to organic synthesis under the supervision of Dr. S. G. Davies in 1986. He then spent 2 years in the laboratories of the late Prof. W. Oppolzer at the University of Geneva, Switzerland, working on the use of sultam auxiliaries in asymmetric organic synthesis. He joined Pfizer Central Research in 1988, where he is currently employed as a Senior Principal Scientist in the cardiovascular area.

Stephen Ballard received a B.Sc. in biochemistry from the University of Bath in 1979. He completed a Ph.D. on the interaction of azole antifungal agents with mammalian hepatic cytochrome P450 enzymes under the supervision of Dr. A. Lodola at the University of Kent in 1988. He then spent 1 year in a postdoctoral research position at Pfizer Central Research working on the development of a cell-free system for studying the ergosterol biosynthetic pathway in the pathogenic fungus *Aspergillus fumigatus*. He took up a permanent post at Pfizer Central Research in 1989, where he is currently employed as a Senior Principal Scientist in the urogenital disease area.

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